BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Fifth Edition

Volume I: Principles and Practice

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San Diego, California

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS, Inc., New York · Chichester · Brisbane · Toronto · Singapore

use of liver microsome preparations as shown for new dopaminergic compounds (245), and to include human microsomes in order to gain some insight into the situation potentially encountered in humans.

8.6 Validity of Classical Pharmacokinetic Concepts for Prodrug Design

As seen in the previous paragraphs, classical pharmacokinetic concepts can be used for the study of prodrugs despite the fact that they have essentially been derived from theoretical considerations related to the situation where the parent compound is the active moiety. As for metabolite kinetics, difficulties arise when the prodrug is not totally biotransformed to the "drug." There is one situation, however, in which it is questionable whether these concepts are fully appropriate, namely drug targeting. For example, if a prodrug is very specifically targeted to one type of cells or to one organ system, it might be necessary to define a "targeting index" to describe distribution of the prodrug and the active moiety, since a concept such as the apparent volume of distribution might only poorly describe the distribution properties of the therapeutic agent. The same restriction may apply to the concepts of systemic availability, systemic clearance and apparent half-life of elimination. This does not mean that classical pharmacokinetic concepts would become invalid, because they are robust and well validated, but that some creativity is probably necessary in order to improve the descriptive power of pharmacokinetics in order to allow comparisons of "drug" and prodrug or between prodrugs. Similar considerations also apply to the concepts basic to biopharmaceutic evaluations. If the necessity to define new pharmacokinetic parameters for the description of targeted prodrugs is accepted, it will be of utmost importance to define only concepts that can be quantified based on experimental data. It is possible that development of imaging techniques such as PET- or NMR-scan will give an impetus to these foreseeable developments in pharmacokinetics.

A problem requiring special attention is the stereoselective *in vivo* activation of prodrugs derived from racemic mixtures, as exemplified by the stereoselective hydrolysis of *O*-acetyl-propanolol (246), for which it was also found that the selectivity of plasma enzyme urase differs from that of liver and intestine enzymes.

9 SOME CONSIDERATIONS FOR PRODRUG DESIGN

9.1 Rationale of Prodrug Design

The design of prodrugs in a rational manner requires, as stated by Bundgaard (9), that the underlying causes which necessitate or stimulate the use of the prodrug approach be defined and clearly understood. It may then be possible to identify the means by which the difficulties can be overcome. The rational design of the prodrug can thus be divided into three basic steps:

- Identification of the drug delivery problem.
- Identification of the physicochemical properties required for optimal delivery.
- Selection of a prodrug derivative that has the proper physicochemical properties and that will be cleaved in the desired biological compartment.

In this context it must be accepted that a very close collaboration is needed between the pharmaceutical chemists active in drug synthesis and those working in the area of xenobiotic metabolism. This is particularly important if more targeted prodrugs are designed in function of enzymes available at the right place, in the right amount and with the right prodrug specificity.

9.2 Practical Considerations

In the rational design and synthesis of prodrugs, several factors should be considered before starting the development of a new compound intended for large-scale production (247):

- The chemical intermediates or modifiers should be available in a high state of purity at reasonable cost.
- Complicated synthetic schemes should be avoided and purification steps should be efficient without markedly increasing production costs. The production should be easy to scale-up from the bench mark to industrial production.
- The prodrug should be stable in bulk form. This is of particular importance for substances like esters, which are likely to be degraded in the presence of even trace amounts of moisture.
- The *in vivo* lability should be efficient to permit release of the active moiety at a rate adequate to ensure its therapeutic activity. Regeneration can be either chemical (pH effects) and/or enzymatic.
- The prodrug and the "carrier moiety" should be nontoxic. Relatively "safe" moieties include amino acids, short to medium length alkyl esters, and some of the macromolecules described previously.
- The pharmacokinetics of the active moiety should be well documented before starting prodrug synthesis, and, at a later stage, prodrug kinetics should be thoroughly investigated in man.
- The biopharmaceutical consequences for prodrug formulations should be carefully evaluated.
- Last but not least, the prodrug should present some clinically relevant advantages over the active principle administered directly. In this context, it must be remembered that modification of one pharmacokinetic property frequently alters other properties of the drug molecule and caution must thus be exercised when embarking on a program of this nature.

10 CONCLUSIONS

Although prodrug design started more than 30 years ago and many reviews have been written on this subject, very little information is available in official guidelines or pharmacokinetic textbooks on the regulatory requirements or data analysis for this type of compounds. This chapter is an attempt to gather and confront available information on the subject.

Some basic problems have, however, been left untouched. For example, the difficulty of extrapolating data from animal to humans encountered during toxicokinetic and toxicologic studies with drugs is amplified with prodrugs since not only metabolism of the active moiety might differ, but also its availability from the prodrug. As a matter of fact, there is presently no published rationale for the conduct of animal and human pharmacokinetic programs during prodrug research and development.

The authors concluded a review on prodrugs (7), quoting the question asked in 1985 (248) by Stella et al.: "Do prodrugs have advantages in clinical practice?" The opinion was the following: "Today, the answer is certainly YES in some particular cases, but for many drugs this aspect of drug design has received no clear and satisfactory solution. The main reason for this situation is that most prodrugs have been synthesized starting from valuable and well-known drugs. As a consequence, the potential advantage of the new chemical entity over its "seasoned precursor" has often been only marginal. It is thus important that in the future, drug design of new chemical entities should incorporate

"delivery and/or targeting components" from the earliest stages of research and development. This strategy might help substances too toxic, or unable to show adequate pharmacologic effects in their basal form to go through primary and secondary screening, before successfully reaching human testing. It is evident that if such an approach were to become an integral part of basic drug design and not just a hindsighted attempt to solve problems associated with older drugs, it would also be necessary to develop new biopharmaceutical and pharmacokinetic approaches to tackle the new challenges." After five years, the authors still believe that this is a valid statement.

After this chapter, which focused more on pharmacokinetic aspects than on chemical synthesis, we can conclude that, indeed, additional thinking on new ways to approach the toxicokinetic and the clinical pharmacokinetics of prodrugs and their active moiety is of paramount importance if prodrug design is to remain (or to become?) an important part for research and development of new therapeutic agents. In parallel, great efforts must be undertaken in order to better understand the molecular basis of xenobiotic metabolism. It should then be easier to synthesize compounds which would show the most appropriate physicochemical characteristics.

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